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Original Articles

Terbutaline inhalations by the Turbuhaler® as replacement for domiciliary nebulizer therapy in severe chronic obstructive pulmonary disease

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Patients with chronic obstructive pulmonary disease (COPD) are often treated with high dose inhalations of β_2-agonists. We compared domiciliary therapy with terbutaline administered by the Turbuhaler® and by a jet nebulizer. Forty nebulizer users with severe COPD were included in the randomized, double-blind, cross-over study. Terbutaline was inhaled t.i.d. for 2 weeks as dry powder (5 doses=2·5 mg) by Turbuhaler® or as solution (2 ml=5 mg) by jet nebulizer (Pari Inhalierboy®). The mean age of the 25 completing patients was 66 years (range: 54–81), the mean FEV_1 was 0·73 l or 29% of predicted (range: 11–55%). The period where the Turbuhaler® delivered the active drug was preferred by 16 patients, the nebulizer period by seven (P=0·09). The median score concerning feeling of control over the disease – according to the Chronic Respiratory Disease Questionnaire – was better after the Turbuhaler® period (P=0·01). Other scores concerning disease related quality of life, the daily peak expiratory flow rates, the additional use of a metered dose inhaler were not significantly different for the two types of treatment. It is concluded that high dose domiciliary terbutaline treatment by Turbuhaler® can replace nebulizer treatment in most patients with severe COPD.

Introduction

The aim of the present study was to compare self administered domiciliary terbutaline therapy by the Turbuhaler® and by a jet nebulizer in COPD patients, who already were on nebulizer therapy. The use of domiciliary nebulizers for administration of high doses of bronchodilators remains controversial (1). In patients with COPD it has been shown that domiciliary β_2-agonist therapy by a nebulizer can be matched by a pressurized metered dose inhaler (MDI) with a 750 ml spacer (2) and even by the MDI alone (3,4). The forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) were found to increase equally well after inhalation of 2 mg terbutaline (four doses) by Turbuhaler® and 5 mg terbutaline from a jet nebulizer when COPD patients inhaled under surveillance of a nurse (5). Most studies on bronchodilators have used changes in the forced expiratory volume as indicators of effect. However, an earlier study found that the subjective relief from terbutaline by a domiciliary nebulizer was unrelated to the reversibility of the airways obstruction in COPD patients (6), and we decided to focus on the subjective relief from the inhalation therapy.

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Patients and Methods

The inclusion criteria were: (a) Domiciliary nebulizer therapy with β_2-agonists daily for at least the previous month, (b) COPD – defined according to American Thoracic Society criteria (7) with $FEV_1 \leq 50\%$ of predicted (national reference values as recommended by the Danish Thoracic Society) – at the most recent test in a stable phase. There were no demands for a specified increase in FEV_1 after a bronchodilator. Users of long term oxygen therapy were not considered for inclusion. Patients with COPD in an unstable phase were likewise not included. The study was in accordance with the

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Helsinki Declaration II, and was approved by the local Ethical Committee.

A randomized, double-blind, cross-over design with a double dummy technique was used. After a 1 week run-in period the patients were randomized to 2 weeks with either treatment A or B followed by 2 weeks with the other. Treatment A was 2·5 mg terbutaline powder (five doses) by Bricanyl® Turbuhaler®+2 ml nebulized isotonic saline three times daily, while treatment B was 2·5 mg lactose powder by Turbuhaler®+2 ml (5 mg) nebulized terbutaline (Bricanyl®) three times daily. We attempted to give equipotent doses of terbutaline as in the previous study (5), and increased the powder dosage from 2·0 mg to 2·5 mg, as the patients should administer the powder inhaler by themselves. The patients continued to inhale by face mask from their own nebulizer: the Pari Inhalierboy®, a jet nebulizer driven by an electrical compressor (the most frequently used brand of nebulizer in Denmark). The patients took one powder dose by maximal inspiration through the powder inhaler after every 10 tidal inspirations from the nebulizer, and after the five powder doses the nebulizer was used until 'dryness'. Oral therapy was not changed during the treatment periods, and a terbutaline MDI was used if extra medication was needed.

After each of the two treatment periods a trained nurse visited the patient. The preferred treatment period was recorded, the general condition marked on a visual analogue scale, and the disease related quality of life measured by a Danish translation of the Chronic Respiratory Disease Questionnaire (8).

At each visit the patient took the same type of inhalation as during the preceding 2 weeks. FEV_1 and FVC were measured by a portable pneumotachograph (Vitalograph Compact®) before and 5, 15, 30 and 60 min after the treatment. The peak inspiratory flow (PIF) and the forced inspiratory volume (FIV) through the powder inhaler were measured by the pneumotachograph during the inhalations. The patients monitored the peak expiratory flow (PEF) before and immediately after each of the three daily treatments (Mini Wright Peak Flow Meter) and recorded the results in a diary together with the number of extra puffs from the MDI. The use of the Turbuhaler® was evaluated by weighing and by checking the position of the indicator wheel. The emptied ampules of nebulizer solution were counted. Poor compliance was defined as inhalation of more than 125% or less than 75% of the prescribed dosage.

The data analysis showed no significant signs of a carry-over effect or a period effect (9) and paired statistical analysis were applied. When a Gaussian distribution of the variable in question could not be excluded a parametric test was performed. Otherwise non-parametric tests were applied. Many zero-differences occurred between the two treatment periods when the quality of life parameters were analysed, and we applied the one-sample Wilcoxon test modified as suggested by Pratt (10).

Table 1 Baseline FEV_1 and FVC (at inclusion into the study), peak inspiratory flow (PIF) and forced inspiratory volume (FIV) through the active Turbuhaler® (average of 5 inhalations for each patient) for the 25 completing patients

	Mean	Range
FEV_1 (l):	0·73	(0·28–1·25)
FEV_1 (% predicted)	29	(11–55)
FVC (l);	1·72	(0·95–3·30)
FVC (% predicted)	51	(30–77)
PIF through the Turbuhaler® ($l\ min^{-1}$)	47	(24–65)
FIV through the Turbuhaler® (l):	1·44	(0·67–2·79)

Table 2 General condition after 2 weeks with the two types of active treatment as scores on visual analogue scales

	Median	Range
Turbuhaler®	67	1–100
Pari Inhalierboy®	48	7–99
Difference (powder inhaler minus nebulizer)	6	−52–64

*The patients answered the question: 'How was your health during the last 2 weeks – everything considered?', 0 mm='worst possible', 100 mm='best possible'. P=0·1485, Wilcoxon signed-ranks test, 95% confidence interval of the median difference: −3 to +25).

Results

Fifteen of the 40 included patients did not complete the study according to the protocol: eight patients due to exacerbation of the COPD (five during active Turbuhaler® treatment), six due to poor compliance, and one patient due to malfunction of the nebulizer. There were no statistically significant differences between completers and non-completers concerning age, smoking habits, duration of nebulizer therapy prior to the study, or maintenance therapy, FEV_1, FVC (before and after terbutaline), or PEF during the run-in period.

Table 3 Results from the Chronic Respiratory Questionnaire: Median scores at interviews after 2 weeks treatment

	Active treatment by					
	Powder inhaler	Nebulizer	*n*	Median difference	95% confidence interval of the difference	*P*
Shortness of breath	16·0	17·0	23	0·0	−3–1	0·591
Fatigue	14·0	14·0	24	0·3	0–2	0·109
Physical function	33·0	31·0	23	0·7	−4–3	0·976
Emotional function	35·5	32·0	24	0·0	−2–2	0·633
Mastery	23·0	21·5	24	0·3	0–2	0·008*
Psychological function	55·0	52·5	24	1·0	−1–4	0·104
Total score	108·0	106·0	23	3·0	−3–5	0·322

Higher scores=better condition. The possible ranges of the scores were 5–35 (shortness of breath), 4–28 (fatigue), 7–49 (emotional function), 4–28 (mastery). The score for physical function was calculated by adding the scores for dyspnoea and fatigue, while the score for psychological function was calculated by adding the scores for emotional function and mastery. The median scores are compared by Wilcoxon–Pratt test.

Table 4 Mean baseline peak expiratory flow, mean increase after inhalation and 95% confidence intervals of the differences (Turbuhaler® minus Pari Inhalierboy®). For each of the 25 patients the average values from the 2 weeks with each treatment are used

	Powder inhaler	Nebulizer	*P* *t*- test	95% confidence interval of the mean difference
Before inhalation ($l\ min^{-1}$)				
Morning	165	167	0·542	−7–3
Afternoon	177	178	0·783	−7–5
Evening	175	174	0·803	−5–7
Increase (% over value before inhalation)				
Morning	16	15	0·101	0–4
Afternoon	13	12	0·633	−1–3
Evening	11	11	0·306	−1–2

The 25 completing patients (16 women and 9 men) had a mean age of 66 years (range; 54–81 years). The median duration of the domiciliary nebulizer therapy prior to the study was 19 months (range: 1–79 months). The data from the baseline expiratory lung function tests and the data from the inspirations through the Turbuhaler® are shown in Table 1. Sixteen patients (70%) preferred the period where the powder inhaler had been active, while seven preferred the active nebulizer period (P=0·0931, binomial test, 95% confidence interval for the preference for Turbuhaler®: 47–87%). The median visual analogue scores concerning the general health condition was higher after the active Turbuhaler® period, but the difference was not statistically significant (Table 2). The median score concerning feeling of control over the chronic disease, was slightly better after the active powder inhaler period, and this difference was statistically significant. However, the summarized scores concerning physical and emotional function were the same after the two types of treatment (Table 3). Baseline PEF and increase in PEF after inhalation were not different for the two types of treatment (Table 4). The baseline FEV_1 and FVC were not different after the two treatment periods nor were the increases in FEV_1 or FVC different (Table 5). Additional use of MDI and the number of reported side effects were not different for the two types of treatment. It was not possible to predict the preferred treatment from the age of the patient, the baseline FEV_1, FVC or from the PIF obtained through the Turbuhaler®.

Discussion

The included patients constituted about 50% of the local nebulizer users fulfilling the inclusion criteria.

Table 5 Mean baseline FEV_1 and FVC and the mean maximal increase over baseline after inhalation at the end of the two treatment periods

	Nebulizer	Powder inhaler	95% confidence interval of the mean difference
FEV_1 (l)	0·69	0·68	−0·03–0·05
FVC (l)	1·67	1·68	−0·13–0·11
Maximal FEV_1 increase (%)	24·2	26·0	−7·2–3·6
Maximal FVC increase (%)	33·0	33·9	−5·3–7·1

Participants in the study were on average 7 years younger and had on average used the nebulizer for a shorter period of time than non-participants. However, the recorded lung function data were not different for participants and non-participants. There were no provable differences between the completers and the non-completers, and the withdrawals were equally distributed between the two types of treatment, which suggests that the conclusions would have been the same if more patients had completed the study.

The statistically significant feeling of better control over the chronic disease during the Turbuhaler® period seems not to have been obtained by chance. The score was calculated from four independent answers, and the differences between two of these were statistically significant, while the other two answers showed the same tendency. Furthermore, the preference data and the scores on visual analogue scales concerning general condition, also showed a tendency towards a better effect from the powder inhaler.

Judged by the 95% confidence intervals of the differences between the remaining quality of life parameters the statistical power of the study was sufficient to exclude differences of clinical importance. Guyatt *et al.* considered an increase in score for physical function of four points or more as clinically important (11).

It was considered impossible to include a period without active treatment in the present study, as all the patients used the nebulizer daily before the study. The present study is unable to evaluate the possible benefit from adding treatment with fixed high doses of bronchodilators in patients with severe COPD. The participants were characterized by daily use of the nebulizer for a long time, suggesting at least substantial subjective relief in this selected group. From the result in this group of selected nebulizer users we conclude that most elderly patients with severe COPD will be able to treat themselves with terbutaline by Turbuhaler® with at least the same benefit as they would obtain from domiciliary treatment by a jet nebulizer. Severe chronic obstruction of the airways does not prevent the use of the powder inhaler, and this treatment should be considered instead of the prescription of a domiciliary nebulizer. The costs of dry powder treatment are considerably less than the costs of domiciliary nebulizer therapy. Furthermore, the patients will benefit from the convenient size of the dry powder device and the short duration of each treatment session.

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